REMARKS

As a preliminary matter, Applicant respectfully notes that 37 CFR § 1.104(b) states that "[t]he examiner's action will be complete as to all matters []." MPEP § 707.07(g) further states that "[p]iecemeal examination should be avoided as much as possible." This standard was not met in the present case. Each one of the pending claims was allowed in the Advisory Action mailed August 12, 2003, yet each is rejected in the present Office Action. The Specification also is objected to for allegedly containing informalities. Each of these rejections and could have been raised when the claims were first presented.[1] Piecemeal examination unfairly increases the time, expense, and uncertainty of prosecution for a patent applicant and reduces the term of a patent that issues from the application. In order to avoid further unnecessary burden and delay, Applicant respectfully requests that the Examiner contact Applicant's undersigned representative by telephone if any of the rejections or objections is maintained, or if further rejections or objections are made, after consideration of the instant Response.

Applicant gratefully acknowledges the telephonic interview granted by Examiners Nickol and Yaen on March 15, 2004, to Applicant and his undersigned representative to discuss the outstanding rejections. The parties discussed the objection and rejections currently pending against Claims 39 and 46-71. Applicant pointed out that the objection to the Specification and the rejection for alleged lack of enablement of Claim 71 both depend on a misreading of the relevant portion of the Application, as explained in detail below. The Examiners apparently agreed that if this were correct then the objection and rejection would be overcome. Applicant informed the Examiners that US Patent Application 2002/0015703 A1 ("Rennert") cannot anticipate Claim 39, and that the cited combination of art cannot make Claims 39 and 46-70 obvious, because Rennert does not teach the identity or structure of the

[1] Each of the art-based rejections relies on US Patent Application 2002/0015703 A1 ("Rennert"), which was cited by Applicant in an Information Disclosure Statement ("IDS") filed September 4, 2003. However, the portion of Rennert cited in the instant rejections is identical to a portion of the related published international application WO 00/42073, which was cited by Applicant in an IDS filed May 11, 2001, and indicated as having been considered in the Office Action mailed July 2, 2002. Thus, even the art-based rejections could have been made when the claims were first presented.

TWEAK receptor (as described in detail below). The Examiners said that an amendment to the claims might overcome these rejections. The parties discussed the possibility of amending the claims in order to overcome the rejection of Claims 39, 46-58 and 71 for alleged lack of written description, but agreement was not reached. Applicant urged that the rejection should be removed with respect to soluble TWEAK receptor polypeptides that bind TWEAK because, consistent with controlling Federal Circuit case law, the disclosure of the instant Application teaches one of skill in the art the structure-function relationship of the recited polypeptides sufficiently to demonstrate possession of them. Agreement was not reached on this point, but the Examiners indicated that a Declaration by the Applicant might overcome this portion of the rejection.

Applicant has amended Claims 39, 46, 59, and 71, and canceled Claim 58, without prejudice, in order to recite the claimed subject matter with greater particularity. The amendments to Claim 39 are supported in the Specification at, for example, page 5, lines 1-3 and page 25, lines 25-30. The amendment to Claim 46 is supported in the Specification at, for example, page 4, line 38 through page 10, line 27, and page 25, lines 28-30. Claims 59 and 71 are amended to change their dependency in light of the cancellation of Claim 58. Claim 59 is further amended to correct a typographical error.

Objection

The Specification is objected to for allegedly inconsistently referring to the TWEAK receptor as both a type I and a type II membrane protein. Applicant respectfully points out that this is incorrect. The cited portion of the Specification (page 2, line 5) states that TWEAK (*i.e.*, the TWEAK *ligand*), not the TWEAK *receptor*, is a type II membrane protein. The Specification consistently refers to the TWEAK *receptor* as a type I membrane protein. Accordingly, Applicant respectfully requests that the instant objection be withdrawn.

Rejections

Rejection under 35 USC § 112, first paragraph (Written Description)

Claims 39, 46-58, and 71 are rejected under 35 USC § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

The written description requirement is satisfied if an application's disclosure informs *one of skill in the art* that the applicant invented the claimed subject matter. *See Union Oil v. Atlantic Richfield*, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow *persons of ordinary skill in the art* to recognize that [he or she] invented what is claimed'" (citation omitted; emphasis added)).

The instant rejection cites *Regents of the University of California v. Eli Lilly Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997; "*Lilly*"). *Lilly* states that describing a claimed genus of chemical compounds " 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Lilly*, 43 USPQ2d at 1405 (quoting *Fiers v. Revel*, 25 USP2d 1601, 1606 (Fed. Cir. 1993)).

But the Federal Circuit has explained that "the *Lilly* disclosure rule does not require a particular form of disclosure [if] *one of skill* could determine from the specification that the inventor possessed the invention at the time of filing" (emphasis added). *Moba v. Diamond Automation*, 66 USPQ2d 1429, 1439 (Fed.Cir. 2003).

Thus, a disclosure of the "functional characteristics [of a genus of claimed genetic material] when coupled with a *known or disclosed correlation between function and structure* [of the claimed genetic material]" provide an adequate written description of the claimed genus of genetic material. *Enzo*, 63 USPQ2d at 1613, (emphasis added) quoting *PTO Written Description Guidelines* ("the *Guidelines*").

The Federal Circuit also has stated that an enabling disclosure of a claimed genus can demonstrate a structure-function relationship sufficient to satisfy the written description requirement without disclosing "the precise 'structure, formula, chemical name, or physical properties'" of the claimed genetic material. *Moba,* 66 USPQ2d at 1439 (citations omitted):

> "[I]n *Enzo* and *Amgen* [*v. Hoechst Marion Roussel*, 65 USPQ2d 1385 (Fed. Cir. 2003)], the record showed that the specification that taught *one of skill in the art* to make and use an invention also convinced that artisan that the inventor possessed the invention."
>
> *Moba*, 66 USPQ2d at 1439 (emphasis added).

Claims 39 and 46, from which each of the other rejected claims ultimately depends, define a TWEAK receptor antagonist as a soluble TWEAK receptor polypeptide that comprises the cysteine-rich repeat and binds TWEAK, an antibody that binds the TWEAK receptor, or an antisense nucleic acid. The instant Specification describes each of these classes of antagonist as required by Federal Circuit case law.

Antibodies that bind the TWEAK receptor

As an example of the rule that a known or disclosed structure-function relationship of a genus of genetic materials provides a written description of the genus, the Federal Circuit stated that the disclosure of the structure of an antigen (*e.g.*, the sequence of an antigenic polypeptide) provides a sufficient written description of the genus of antibodies that bind to the antigen. *See Enzo*, 63 USPQ2d at 1613; *see also* the *Guidelines*, Example 16. Because of the known relationship between structure and function for antibodies, the disclosure need not teach the structure of even one specific antibody within the genus, much less a "representative number of species." See *id.* The instant Specification provides, *inter alia*, the complete amino

acid sequence of the TWEAK receptor. Consequently, the instant Specification describes the class of antibodies that bind to the TWEAK receptor. Accordingly, Applicant respectfully requests that the instant rejection be withdrawn with respect to methods of using antibodies that bind the TWEAK receptor.

Antisense nucleic acids

Under the same principle adopted by the Federal Circuit in *Enzo* with respect to the written description of antibodies, the *Guidelines* state that the disclosure of a mRNA (*i.e.*, a cDNA) sequence provides a written description of the genus of antisense nucleic acids against it. *See* the *Guidelines*, Example 15. The instant Specification provides, *inter alia*, the complete cDNA sequence of the TWEAK receptor. See the Specification at, for example, page 25, lines 25-26 and SEQ ID NO:3. Thus, the instant disclosure describes the genus of antisense nucleic acids recited in the rejected claims. Consequently, Applicant respectfully requests that the instant rejection be withdrawn with respect to methods of using antisense nucleic acids.

Soluble TWEAK receptor polypeptides that comprise the cysteine-rich repeat and bind TWEAK

The instant specification, combined with the knowledge of one skilled in the art, satisfies the written description requirement of *Lilly*, *Enzo*, *Amgen*, and *Moba* for the genus of soluble TWEAK receptor polypeptides that comprise the cysteine-rich repeat and bind TWEAK by providing an enabling disclosure that elucidates their structure-function relationship.

The Specification teaches the function of the recited polypeptides

The stated function of the recited polypeptides is to bind TWEAK. The Specification teaches assays for determining whether a polypeptide binds to TWEAK, and correlates binding of TWEAK to inhibiting the TWEAK receptor *in vivo*, at, for example, page 19, line 33 through page 24, line 31, page 27, line 33 through bottom

of page 28 and page 29, line 30 through page 31, line 5. Thus, the instant Specification teaches the *function* of the recited polypeptides.

The Specification teaches the structure of the recited polypeptides

The present Specification provides the sequence of, *inter alia*, the TWEAK receptor extracellular domain. See, for example the Specification at page 25, lines 25-28, page 27, lines 1-8 (disclosing the sequence of the signal peptide), and SEQ ID NO:4. The Specification also teaches that the extracellular domain comprises a single cysteine-rich repeat. See the Specification at, for example, page 25, lines 30-31 and SEQ ID NO:4. The Specification further teaches the identity and sequence of TWEAKR-Fc, an example of the recited polypeptides. See, for example, the Specification at 26, line 30 through page 27, line 10. The Specification further teaches how to make polypeptides comprising soluble portions of the extracellular domain of the TWEAK receptor. See the Specification at, for example, page 4, line 38, through page 9, line 3. Thus, the Specification teaches the *structure* of the recited polypeptides.

The Specification teaches the structure-function relationship of the recited polypeptides

The Specification also correlates the structure of the recited polypeptides with the function of binding TWEAK. See, for example, the Specification at page 27, line 33 through bottom of page 28; page 29, line 30 through page 31, line 5, which teaches assays for testing the ability of soluble TWEAK receptor polypeptides to bind to TWEAK, assays that correlate binding of TWEAK to inhibiting TWEAK receptor activity *in vivo*, and specific working examples of the assays using TWEAKR-Fc.

Accordingly, the Specification discloses the structure of the recited polypeptides, their function, and their structure-function relationship.

The knowledge in the art provides more information about the structure-function relationship of the recited polypeptides

The Specification must be considered not merely for what it explicitly discloses, but for what its disclosure means to *one of skill in the art. Union Oil*, 54 USPQ2d at 1227; *Moba*, 66 USPQ2d at 1439. Significantly, the Specification reveals for the first time that the TWEAK receptor is a member of the tumor necrosis factor receptor super family ("TNFRSF") and that its extracellular domain contains one copy of a cysteine-rich repeat, a motif that is common to the TNFRSF. See the Specification at, for example, page 25, lines 30-32. This information gives one of skill in the art a detailed understanding of the structure and function of the recited polypeptides.

As of the priority date of the instant Application, it was well known that the *function* of the extracellular domains of the TNFRSF is binding ligand. See the attached Declaration of Dr. Steven Wiley; see also Naismith *et al.*, 1998, TIBS 23:74-79; Lotz *et al.*, 1996, J Leukoc Biol. 60:1-7; Bazzoni *et al.*, 1996, New England J Med. 334:1717-25; Naismith *et al.*, 1996, J Inflamm. 47:1-7; van Ostade *et al.*, 1994, Protein Eng. 7:5-22; Wallach *et al.*, 1991, Agents Actions Suppl. 35:51-57.

The *structure* of the TNFRSF extracellular domain also was well known. See the attached Declaration of Dr. Steven Wiley; see also Naismith (1998), and Naismith (1996). The extracellular domains of many TNFRSF members have only a low level of overall amino acid sequence similarity to each other. See Naismith (1996) at column 2, page 2. However, the family is characterized by the presence of one to six copies of an approximately 40 amino acid residue cysteine-rich repeat motif in the extracellular ligand binding domain. See, for example, Lotz *et al.* at page 1, column 1. The consensus sequence for these cysteine-rich repeats is Cys1-x_{10-15}-Cys2-x_2-Cys3-x_2-Cys4-x_{8-11}-Cys5-x_{7-8}-Cys6, see Naismith (1996) at page 6, although more distantly related members of the superfamily deviate somewhat from this formula, see *id.* These cysteine residues form a network of disulfide bonds that gives the TNFSF ligand binding domains a characteristic tertiary structure, in spite of their diverse primary sequences. See Naismith (1998) at column 1, page 74.

The TWEAK receptor cysteine-rich repeat has the sequence Cys1-x_{12}-Cys2-x_2-Cys3-x_2-Cys4-x_8-Cys5-x_2-Cys6, which is very close to the consensus sequence. See the Specification at, for example, Figure 1.

The *structure-function relationship* of the TNFRSF extracellular domains also was well known. Specifically, at least three lines of evidence showed that TNFRSF members bind ligand via their cysteine-rich repeats.

First, X-ray crystallographic analysis of the extracellular domain of TNF receptor bound to ligand showed that the ligand was bound to cysteine-rich repeats of the extracellular domain. See Naismith (1996) and Naismith (1998).

Second, soluble, ligand-binding fragments of TNFRSF members were known in the art. As early as 1996, the list of TNFRSF members known to have *naturally-occurring* ligand-binding soluble forms included TNFR1, TNFR2, Fas, CD27, CD30, CD40, 4-1BB, and NGFR. See Lotz at Table 1. Other soluble TNFRSF homologs were known to be expressed by viruses and to suppress the host immune response by binding and sequestering TNF. See Naismith (1998) at column 1, page 74. Furthermore, as of the instant Application's priority date,

> [r]ecombinant forms of the soluble receptors that contain the entire extracellular regions *or parts thereof* [were] important tools in characterizing the biological functions of the TNF-R and [were] under investigation as therapeutic agents in sepsis, arthritis, and other conditions.

Lotz at page 2 (citation omitted; emphasis added). One such molecule, etanercept (ENBREL®, Amgen, Inc., Thousand Oaks, CA), a soluble TNF receptor comprising cysteine-rich repeats, was so well characterized that in 1998 the United States Food and Drug Administration approved it for therapeutic use in humans. See Garrison *et al*, 1999, Ann Rheum Dis 58 (Suppl I):I65-I69. According to the

ENBREL® website (www.enbrel.com/index.jsp), since its approval, ENBREL® has been used by over 200,000 people.

Third, deletion analysis of osteoprotegrin ("OPG"; also known as osteoclastogenesis inhibitory factor), a naturally occurring soluble TNFRSF member, showed that mutated OPG with intact cysteine-rich repeats bound to ligand, but that mutated OPG with disturbed repeats did not. See Simonet *et al.*, 1997, Cell 89:309-19, Figure 5C and page 315 ("[T]he N-terminal portion of OPG containing the TNFR-like domain [*i.e.*, the cysteine-rich repeats] is *necessary and sufficient* to inhibit osteoclastogenesis."); Yamaguchi *et al.*, 1998, J Biol Chem 273:5117-23, Figure 1 and page 5119 (Deletion mutants "ΔD3 and ΔD4 [each of which is missing a portion of the cysteine-rich repeat] failed to inhibit the osteoclast-like cell formation []. In contrast, ΔD5 [a deletion mutant with an intact cysteine-rich repeat region] retained the inhibitory activity [].").

Thus, as of the priority date of the instant Application, one of skill in the art knew that for TNFRSF members the *function* of binding ligand is mediated by the *structure* of cysteine-rich repeats. Therefore, the instant Specification teaches one of skill in the art the structure-function relationship for the recited polypeptides. Consequently, the instant Specification describes the recited polypeptides. Accordingly, Applicant respectfully requests that the instant rejection be withdrawn with respect to the recited polypeptides.

Rejection under 35 USC § 112, First Paragraph (Enablement)

Claim 71 is rejected under 35 USC § 112, first paragraph, for allegedly lacking enablement. It is asserted that the Specification at page 2, line 5, teaches that the TWEAK receptor is a type II membrane protein wherein the C-terminal domain is the extracellular portion. As explained above, the quoted passage teaches that TWEAK (*i.e.*, the TWEAK *ligand*) is a type II membrane protein. It says nothing at all about the structure of the TWEAK *receptor*. Consequently, the instant rejection

relies on a misreading of the Specification and therefore is moot. Accordingly, Applicant respectfully requests that the instant rejection be withdrawn.

Rejection under 35 USC § 102 (e)

Claim 39 is rejected under 35 USC § 102(e) for allegedly being anticipated by US Patent Application 2002/0015703 A1 ("Rennert"). Applicant respectfully traverses.

In order to anticipate a claim, a reference must, *inter alia*, enable the claim. *See In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980); *Amgen v. Hoechst Marion Roussel*, 65 USPQ2d 1385, 1416-17 (Fed. Cir. 2003). Enablement requires that the invention can be practiced by one of ordinary skill in the art without undue experimentation.

Rennert purports to teach antagonists of the TWEAK receptor. In fact, Rennert not only fails to teach any such antagonists, it actually *misidentifies* the TWEAK receptor. Rennert states that

> [a] putative receptor for TWEAK has been described (Marsters et al., *Curr. Biol.* 8 525-28 (1998)) []. This receptor, variably known as TRAMP, Apo3, WSL-1, DR-3, or LARD is a member of the TNF-R family. Activation of TRAMP can induce apoptosis [].
>
> Rennert, page 4, paragraph [0041].

But the instant Specification proves that DR3, the molecule that Marsters claimed is the TWEAK receptor, is *not* the TWEAK receptor:

> The newly identified TWEAK receptor was tested side by side with DR3 (which had been identified as the TWEAK receptor by Marsters [citation omitted]) for the ability to bind to TWEAK.
>
> ...

> Slides of COS cells were transfected with expression vectors containing TWEAKR, DR3, or vector without insert (control). After two days the cells were incubated with [soluble TWEAK ligand]. The TWEAKR transfected cells bound significant amounts of TWEAK. *TWEAK did not bind to the cells transfected with DR3* or the control cells."
>
> Specification, page 25, line 37 through page 26, line 11 (emphasis added).

Thus, DR3, the molecule that Rennert claimed was the TWEAK receptor, does not bind to TWEAK. Consequently, it is not the TWEAK receptor. Accordingly, Rennert does not teach the structure or identity of the TWEAK receptor. Without that critical information—which was revealed for the first time in the instant Specification and its siblings—one could not practice the rejected claims. Hence, Rennert does not enable the methods of the rejected claims. A reference cannot anticipate a claim that it does not enable. See *Sasse* and *Amgen*. Thus, Rennert does not anticipate the rejected claims. Applicants respectfully request that the instant rejection be withdrawn.

Rejection under 35 USC § 103(a)

Claims 39 and 46-70 are rejected under 35 USC § 103(a) as allegedly obvious over Rennert in view of Lynch *et al.*, Miller, 1998, Surg. Oncol. Clin. N. Am. 7:183-97 and US Patent 5,677,181 ("Parish"). Applicants respectfully traverse.

A *prima facie* case of obviousness requires, *inter alia*, that the cited references provide one of ordinary skill in the art with a reasonable expectation of success in achieving the claimed invention. *See Amgen v. Chugai Pharmaceutical*, 18 USPQ2d 1016, 1022-23 (Fed. Cir. 1991). A *prima facie* case of obviousness can be overcome by, for example, providing references that teach away from the claimed invention. *See W.L. Gore & Associates v. Garlock*, 220 USPQ 303 (Fed. Cir. 1983).

As explained above, Rennert does not teach the identity or structure of the TWEAK receptor. Without this critical information, provided for the first time in the instant application and its siblings, one of skill in the art would not have a reasonable expectation of successfully practicing the claimed methods of the rejected claims. Consequently, a *prima facie* case of obviousness has not been made.

Furthermore, Rennert actually *misidentifies* DR3 as the TWEAK receptor, as explained above. One of skill who followed the teachings of Rennert would, at best, attempt to make antagonists of DR3. But, as the instant Specification proves, *DR3 is not the TWEAK receptor*. See above. Thus, Rennert actually teaches away from the claimed invention.

Accordingly, Applicant respectfully requests that the instant rejection be withdrawn.

CONCLUSION

Applicant believes that the application is in condition for allowance. An early and favorable action on the merits is earnestly solicited. If a fee is required in connection with this paper, please charge Applicant's Deposit Account No. 09-0089 in the amount necessary to permit consideration of this amendment and response.

Respectfully submitted,

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